Remarks

After amendment, claims 6-9 and 25-30 remain pending in the present application, claims 10-24 having been cancelled previously *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's decision to elect with traverse to prosecute the invention of original claims 1-9. Claims 1-5 have been cancelled previously *without prejudice* in order to seek expedited allowance of the instant application. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter previously cancelled.

The amendments to the claims have been made to indicate that the present methods are directed to the use of noribogaine as a non-addictive analgesic agent to treat nocicpetive pain with an opioid agonist (as an anti-nociceptive agent) without the addiction typical of opioid agonist analgesics such as morphine. Thus, the present invention in claims 25-30 is essentially directed to the use of noribogaine as a substitute for morphine (or other opioid agonist) as an analgesic in the treatment of nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency. Claims 6-9 are directed to the use of noribogaine in combination with at least one opioid antagonist in the treatment of nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency. Support for the amendment to the claims can be found throughout the originally filed application and claims and in particular, at page 3, first, second and third paragraphs, in particular at line 4 and lines 12-16, page 4, lines 14-15, page 6, first paragraph and in particular, lines 4-5, page 7, first paragraph, especially lines 4-5, page 8, especially pages 4-12 (treatment of pain in the absence of withdrawal symptoms associated with drug dependency) and on page 9 in the examples section and in particular in the last paragraph at lines 20-23 (noribogaine is a full agonist of the receptor, acts as an antinociceptive agent in the treatment of nociceptive pain without the abuse liability inherent to opiates. No new matter has been added by way of the present amendment.

Note that in addition to the specification clearly indicating that noribogaine is a full opioid agonist, the specification also clearly indicates that noribogaine is also an antinociceptive agent (i.e., an agent which eliminates or reduces nociceptive pain). See page

9, lines 20-23. Thus, the present application is directed to the unexpected discovery that noribogaine is a full opioid receptor agonist which acts as an antinociceptive agent, exhibiting antinociceptive activity similar to morphine's activity, without morphine's addiction to the patient. Thus, the present invention represents a clear advance in the art and is deserv ing of patent protection.

The term "consisting essentially of" as presented in claim 25 is used to describe a composition which contains noribogaine but which is non-addictive (i.e., does not have the addictive properties of typical opioid agonists such as morphine). Thus, compositions which may be used in the method of claim 25 and claims dependent thereon may contain an effective amount of noribogaine and any additional component which does not change the basic and novel characteristics of the compositiosn which is directed to the ability to treat nociceptive pain without addiction. Thus, compositions which consist essentially of noribogaine contain noribogaine as an active and may contain other components or agents provided that the composition used to treat pain is essentially non-addictive, i.e., excludes typical addictive opioid agonists such as morphine.

The present invention is directed to the use of noribogaine as an antinociceptive agent, similar to the effects obtained with morphine, but without the liability of abuse which occurs with typical opioid agonists such as morphine. Nociceptive pain, as distinguished from neuropathic pain, is pain which is mediated through nociceptors. See the enclosed definition of nocicpetive and nociceptors which is from Stedman's Medical Dictionary, 26th Edition, as well as the discussion of nociceptive pain from gp-training.net at gp-training.net/rhyum/pain.htm, a British physician training site for general practitioners. Morphine, as an analgesic, acts as a receptor agonist to alleviate pain which is mediated through nociceptors or nociceptive pain. In contrast, neuropathic pain is a chronic pain which occurs due to injury to nervous tissue. Neuropathic pain is completely distinguishable from nociceptive pain in the art.

Note that the present claims are directed to a method of treating nociceptive pain in the absence of withdrawal symptoms associated with chemical dependency in order to address any possible *inherency or obviousness* issues which may be raised by any of the cited prior art. It is respectfully submitted that the present invention is the first instance of noribogaine being

used as a non-addictive antinociceptive agent in the absence of withdrawal symptoms associated with drug dependency. The art clearly failed to appreciate that noribogaine possesses antinociceptive activity as a full receptor agonist and can be used as a non-addictive analgesic agent possessing pharmacological activity similar to morphine without the addictive side affects of morphine. The present invention, as presently claimed, therefore represents an unexpected result. The present invention is patentable.

The Examiner, having considered the previously filed amendment/response, has withdrawn all rejections from the previous office action. In the office action dated January 13, 2006, the Examiner has newly rejected the previously submitted claims variously under 35 U.S.C. §103 and the cited prior art. For the reasons which are presented hereinbelow, it is respectfully submitted that the instantly amended claims are non-obvious over the cited prior art.

The Rejection of the Previously Filed Claims under 35 U.S.C. § 103

The Examiner has rejected the previously filed claims as being unpatentable under 35 U.S.C.§103. It is the Examiner's contention that the previously presented claims are obvious over the newly cited art, inasmuch as the Examiner believes that a number of combinations of references teaches that ibogaine or noribogaine can be used to treat withdrawal symptoms in a patient and consequently, that treatment of withdrawal symptoms of the patient will result in the withdrawal patient's pain symptoms also being treated by noribogaine, either directly or as a metabolite of ibogaine. Alternatively, the Examiner cites US Patent no. 5,925,634 to Olney ("Olney") and "Properties of Ibogaine and Its Principle Metabolite (12-hydroxyibogamine) at the MK-801 Binding Site of the NMDA Receptor Complex" to Mash, et al. ("Mash, et al") as teaching that noribogaine may be used to treat neuropathic pain in a patient. Note that to distinguish all of the art and all of the Examiner's rejection is the fact that the claims are now limited to the treatment of nociceptive pain in a patient in the absence of withdrawal symptoms.

It is respectfully submitted that there is absolutely no motivation in the art to treat nociceptive pain in a patient in the absence of withdrawal symptoms with noribogaine or with noribogaine and an opioid antagonist as presently claimed. Consequently the instant invention

is patentable over the cited art.

The Rejection of Claims 25-30 Over U.S. Patent No. 5,591,738, in view of Applicant's Admissions

As discussed above, the Examiner has cited the '738 patent in combination with Applicant's own statements as rendering the present invention obvious. Essentially, the Examiner has argued that the '738 patent teaches that noribogaine may be used to treat drug withdrawal and that certain types of pain are associated with drug withdrawal. Thus, the Examiner argues, the use of noribogaine for the treatment of withdrawal symptoms in a patient will result in the patient's pain associated with withdrawal being treated. In contrast, the newly presented claims are non-obvious over the teachings of the prior art inasmuch as there is absolutely no teaching, suggestion or motivation to use noribogaine in the absence of withdrawal symptoms to treat nociceptive pain.

The Rejection of Claims 25-30 Over Pablo, et al., in view of Applicant's Admissions

The Examiner has cited the reference "Noribogaine Stimulates Naloxone-Sensitive [^{35}S] GTP S Binding" by Pablo, et al. ("Pablo, et al.") in view of Applicant's own admissions to reject the previously submitted claims as being obvious under 35 U.S.C.§103 for the reasons stated in the office action on pages 8-9. Essentially, the Examiner argues that Pablo, et al. teaches that noribogaine is a metabolite of ibogaine and that ibogaine can be used to block the acute signs of opiate withdrawal and that certain types of pain are associated with drug withdrawal. Thus, the Examiner argues, the use of ibogaine for the treatment of withdrawal symptoms in a patient will result in the patient's pain associated with withdrawal being treated.

First, it is noted that Pablo, et al. is not prior art against the instant invention inasmuch as Pablo, et al. was published in January, 1998 (not December 20, 1997 as indicated by the Examiner) and the present invention was originally filed as provisional application no. 60/057,921, several months before the filing date of the putative prior art. It is also noted here that the inventor of the instant application, Dr. Deborah Mash, is also a co-author of Pablo, et al.

Notwithstanding the fact that Pablo, et al. is not prior art to the present invention, it is quite clear from the teachings of the references that the newly presented claims are non-obvious over the teachings of the prior art inasmuch as there is absolutely no teaching, suggestion or motivation to use noribogaine in the absence of withdrawal symptoms in a patient to treat nociceptive pain.

Regarding the Examiner's discussion of the term "consisting essentially of", this term is slightly narrower than the term "comprising" in that the term excludes components or actives which change the basic and novel characteristics of the compositions used in the method of claim 25 which is directed to the treatment of nociceptive pain in the absence of withdrawal symptoms without addiction. Thus, agents which produce addiction in the treated patient are excluded from the compositions of claim 25 and claims dependent thereon.

The Rejection of Claims 25-30 Over The Mash Patent, in view of Applicant's Admissions

The Examiner has cited U.S. patent no. 6,348,456 to Mash, et al. ("the Mash patent.") in view of Applicant's own admissions, to reject the previously submitted claims as being obvious under 35 U.S.C.§103 for the reasons stated in the office action on pages 11-15. Essentially, the Examiner argues that the Mash patent teaches that essentially pure noribogaine can be administered for the treatment of chemical dependency and that such treatment will result *inherently* in the treatment of pain secondary which occurs secondary to chemical dependency/withdrawal. In contrast, the newly presented claims are non-obvious over the teachings of the prior art inasmuch as there is absolutely no teaching, suggestion or motivation to use noribogaine in the absence of withdrawal symptoms in a patient to treat nociceptive pain.

The Rejection of Claims 25-30 Over Mash, et al., in view of Applicant's Admissions

The Examiner has cited "Properties of ibogaine and its Principle Metabolite (12-hydroxy ibogaine (noribogaine) at the MK-801 Binding Site of the NMDA Receptor Complex" (Mash, et al.) in view of Applicant's own admissions, to reject the previously submitted claims

as being obvious under 35 U.S.C.§103 for the reasons stated in the office action on pages 15-19. Essentially, the Examiner argues that Mash, et al. teaches that ibogaine and its principle metabolite, noribogaine, act as antagonists to the MK-801 binding site of the NMDA receptor, and consequently can act to treat withdrawal symptoms from chemical dependency. Thus, the Examiner argues that Mash, et al. teaches that noribogaine can be administered for the treatment of chemical dependency and that such treatment will result *inherently* in the treatment of pain secondary to the withdrawal symptoms. In stark contrast, the newly presented claims are non-obvious over the teachings of the prior art inasmuch as there is absolutely no teaching, suggestion or motivation in the art to use noribogaine in the absence of withdrawal symptoms in a patient to treat nociceptive pain.

The Rejection of Claims 25-30 Over Olney, in view of Mash, et al.

The Examiner has cited US Patent No. 5,925,634 to Oley, et al. ("Olney") in view of Mash, et al. (cited above) against previously submitted claims 25-30 of the instant application. The Examiner argues that because Olney teaches that ibogaine may be used to treat neuropathic pain by functioning as an NMDA antagonist and Mash, et al. teaches that both ibogaine and noribogaine exhibit antagonistic activity against NMDA receptor, that noribogaine may be used to treat neuropathic pain.

Olney, in view of Mash, et al. in no way renders the present invention obvious. In the first instance, the claims are directed to the treatment of nociceptive pain, not neuropathic pain, completely distinguishable types of pain. The art, including Olney, well recognizes that ibogaine is not useful in the treatment of nociceptive pain. Mash, et al., contrary to the Examiner's contention, does not teach that noribogaine may be substituted for ibogaine in the treatment of neuropathic pain as an NMDA receptor antagonist, but rather, that noribogaine, because of its *4-6 fold lower potency at the NMDA receptor and its reduced dwell time* in the ion channel at the receptor site (page 55, second column), is *not to considered useful as a* neuropathic agent.

Indeed, as shown by Mash et al., noribogaine has no physiologically relevant actions at NMDA receptors. This is demonstrated by the lack of a physiological effect. Concentrations were in excess of 1 mM and therefore would never be reached by the suggested dose

schedule. This is at least *1,000 fold excess*. Thus, noribogaine exibits no dwell time in the channel and therefore no activity. The hallucinogenic and neurotoxic effects are due to the action of ibogaine at the NMDA receptor site. Indeed, Mash, et al., stands for the proposition that noribogaine may be more appropriate as an anti-addictive agent than ibogaine precisely because noribogaine does ***not*** have the potent neurotoxic properties of ibogaine. Thus, if anything, Mash, et al., *teaches away* from using noribogaine as a neuropathic agent because it is substantially less active/inactive than ibogaine in this regard.

Moreover, neither Olney, nor Mash, et al. teach nor even remotely suggest noribogaine as an effective agent for use to treat nociceptive pain as a non-addictive substitute for morphine. Given that the combined teachings of Olney and Mash, et al. teach away from the use of noribogaine as a *neuropathic* agent and do not even mention ibogaine or noribogaine as antinociceptive agent, the present invention is clearly non-obvious and patentable over the teachings of Olney, in view of Mash, et al.

The Rejection of Claims 6-9 over Lotsof, in view of Applicant's Own Admissions and Further in view of Archer

The Examiner has rejected previously filed claims 6-9 as being obvious over Lotsof, inview of Applicant's admissions and further in view of Archer. Claims 6-9 are directed to the use of norobigaine in combination with at least one opioid antagonist to treat nociceptive pain in the absence of withdrawal symptoms without addiction. For the reasons set forth hereinabove, the combined teachings of Lotsof and Applicant's own admissions do not teach or suggest the use of noribogaine to treat nociceptive pain without addiction in the absence of withdrawal symptoms in a patient. Archer, which simply teaches that an opioid antagonist may be used to treat withdrawal symptoms associated with certain (not pain), does not in any way obviate the fact that the cited art does not render the present invention obvious. The use of noribogaine to treat nociceptive pain without addiction in combination with one or more opioid antagonist(s) is simply not disclosed nor even remotely suggested by the combined art.

Archer teaches the use of naltrexone as a treatment for psychostimulant dependence, not opioid dependence. There is no nociceptive pain generally associated with psychostimulant dependence.[1] He bases this on the effects of naltrexone on blocking rat self-administration of cocaine. This is thought to reflect a change in the reinforcing efficacy of cocaine. There is no other information provided.

Contrary to the Examiner's contention, one of ordinary skill would not have known to use a combination of noribogaine plus natrexone for pain control, because pain is not a secondary symptom or feataure of the psychostimulant withdrawal taught to be treated by Archer. Indeed there is absolutely no teaching in Archer of the use of an opiate antagonist for the treatment of opiate withdrawal and there is obviously no basis for combining Archer with Lotsof to treat pain. To the extent that there is teaching to treat psychostimulant withdrawal by Archer, that treatment will not result in the treatment of pain.

The rationale for the combination of use in the present invention is based upon the effects of noribogaine as agonist in treating nociceptive pain without addiction and in the absence of withdrawl symptoms. The present invention is not disclosed or suggested by cited prior art.

The Rejection of Claims 6-9 over Pablo, et al, in view of Applicant's Own Admissions and Further in view of Archer

The present invention is clearly patentable over the combined disclosures of Pablo, et al. and Applicant's own admissions for the reasons which are stated hereinabove. In the first instance, Pable, et al., as explained hereinabove, is not prior art to the present application. Separately, notwithstanding the fact that Pablo, et al. is not prior art, the present invention, which relates to the use of noribogaine to treat nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency is clearly patentable over these combined disclosures of Pablo, et al. and Applicant's admissions. Archer fails to add substantively to the other teachings. Archer teaches the use of opioid antagonists for treating withdrawal symptoms associated with certain types of drug (psychostimulant) dependency, but

1 Note that Archer, at column 2, lines 50-58 provides the general symptomology/physiology associated with amphetamine or cocaine withdrawal., which includes "hunger and prolonged sleep.. depression, general fatigure and a marked increase in rapid eye movement ("REM") sleep."

not pain. In no way can the combined disclosures be taken to render the present invention obvious, inasmuch as it was unknown in the art to use noribogaine to treat nociceptive pain and it was unknown to use noribogaine in the absence of withdrawal symptoms. The further disclosure of Archer in no way obviates the combined disclosures given that the treatment of psychostimulant withdrawal symptoms does not result in the treatment of pain without addiction in the absence of withdrawal symptoms. The combined teachings of the prior art can in no way be taken to render the invention of claims 6-9 obvious.

The Rejection of Claims 6-9 over the Mash patent, in view of Applicant's Own Admissions and Further in view of Archer

The present invention is clearly patentable over the combined disclosures of the Mash patent and Applicant's own admissions for the reasons which are presented hereinabove- there is simply no disclosure or even a remote suggestion of the use of noribogaine for treating nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency. The present invention, which in claims 25-30 relates to the use of noribogaine, further in combination with at least one opioid antagonist (claims 25-30) to treat nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency, is clearly patentable over these combined disclosures. Archer, also cited here, fails to add substantively to the other teachings. Archer teaches the use of opioid antagonists for treating withdrawal symptoms associated with psychostimulant drug dependency (which, as discussed above, does not have nociceptive pain as a secondary characteristic), but not pain. There is simply no disclosure, suggestion or motivation to combine these references to produce the present invention as claimed in claims 25-30. In no way can the combined disclosures be taken to render the present invention obvious.

The Rejection of Claims 6-9 over the Mash, et al., in view of Applicant's Own Admissions and Further in view of Archer

The present invention is clearly patentable over the combined disclosures of Mash, et al. and Applicant's own admissions for the reasons which are presented hereinabove- there is simply no disclosure or even a remote suggestion of the use of noribogaine for treating nociceptive pain without addiction in the absence of withdrawal symptoms associated with

drug dependency. The present invention, which in claims 25-30 relates to the use of noribogaine, further in combination with at least one opioid antagonist (claims 25-30) to treat nociceptive pain without addiction in the absence of withdrawal symptoms associated with drug dependency, is clearly patentable over these combined disclosures. Archer, also cited here, as discussed above, fails to add substantively to the other teachings. Archer teaches the use of opioid antagonists for treating withdrawal symptoms associated with psychostimulant (not opioid) drug dependency (which itself does not feature nociceptive pain as a secondary characteristic), but not pain. There is simply no disclosure, suggestion or motivation to combine these references to produce the present invention as claimed in claims 25-30. In no way can the combined disclosures be taken to render the present invention obvious.

Further Comments

On pages 32-34 of the January 13, 2006 office action, the Examiner has presented a response to the arguments which were made in the previous amendment/response filed December 22, 2005 in the present application. It is respectfully submitted that the presently amended claims and arguments presented herein fully address each of the Examiner's concerns. It is also respectfully submitted that the presently amended claims do present the unexpected result of noribogaine (and further in combination with an opioid antagonist) being useful for treating nociceptive pain in a patient without addiction associated with a typical opioid agonist such as morphine in the absence of withdrawal symptoms associated with drug abuse. The invention is clearly non-obvious over all of the cited art and is patentable.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have not added nor cancelled any claim. No fee is therefore due for the presentation of this amendment. A petition for a one month extension of time is enclosed as is a check in the amont of $55. If any fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838. Should the Examiner wish to discuss the present application in an effort to advance its prosecution, the undersigned attorney may be reached at the telephone number set forth hereinbelow. A supplemental information disclosure based upon art cited in a corresponding Canadian application was sent previously to the patent office under separate cover.

Respectfully submitted,
Coleman Sudol Sapone, P.C.

By: _____
Henry D. Coleman
Regis. No. 32,559
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
(203) 366-3560

Enclosures

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "United States Patent and Trademark Office P.O. Box 1450 Alexandria, Virginia 22313-1450" on April 21, 2005.

_____
Henry D. Coleman